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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,308	01/02/2002	Hugo A.G. Geerts	JAB-1515	8790

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,308	GEERTS ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44 and 49-51* is/are pending in the application.

4a) Of the above claim(s) *12-19,24-44 and 49-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

Applicant's amendment filed on 05/13/2004 has been entered. Claims 1,6 and 20 have been amended. Claims 45-48 have been cancelled. Claims 12-19, 24-44 and 49-51 have been withdrawn as being drawn to a non-elected invention. Claims 1-44 and 49-51 are pending and claims 1-11 and 20-23 are under consideration in the instant action. Claims

Revised Amendment Practice

The amendment to the claims filed 05/13/04 is not compliant with the revised amendment practice. The status identifier of claim 6 should read "Currently Amended". The status identifier of claims 10 and 11 should read "Previously Presented".

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a nucleic acid vector comprising a nucleic acid sequence encoding a human Tau protein operably linked to a sequence that directs expression of said human Tau nucleic acid in the nervous system wherein the sequence directing expression is the Thy1 promoter and wherein the vector is capable of integrating into the endogenous Tau equivalent gene of a mouse and for 2) an in vitro isolated, pluripotent or lineage restricted host cell transformed, transfected or injected with a vector comprising a nucleic acid sequence

encoding a human Tau protein operably linked to a sequence that directs expression of said human Tau nucleic acid in said cell wherein the sequence directing expression is the Thy1 promoter and wherein the vector is capable of integrating into the endogenous Tau equivalent gene, does not reasonably provide enablement for any sequence capable of directing expression of said human Tau nucleic acid in the nervous system or a vector wherein said vector can be targeted to the tau gene in the genome of any species of non-human animal, wherein said vector prevents expression of the endogenous Tau equivalent gene or 2) a cell in vivo or any totipotent cell comprising the claimed vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are drawn to a nucleic acid vector comprising a nucleic acid encoding a human Tau protein, a nucleic acid capable of directing expression of human Tau in the nervous system of non-human animals and a targeting sequence that allows integration of the vector into the endogenous Tau gene of said non-human animal. Claims are also directed to cells, both in vivo and in vitro, comprising said vector.

The specification discloses that human Tau has a role in Alzheimer's disease because when hyperphosphorylated, it aggregates to form inclusion bodies, a characteristic of Alzheimer's disease (specification, page 1, paragraph 3). Thus, the specification teaches using nucleic acids and transgenic mice to model Alzheimer's disease by causing the hyperphosphorylation of human Tau and formation of inclusions in the neurons of doubly transgenic mice comprising a first transgene encoding human Tau inserted into and disrupting the mouse Tau gene and a second transgene encoding a kinase that leads to human Tau

hyperphosphorylation. The asserted utility of the claimed nucleic acid vector is in generating a transgenic animal model of Alzheimer's characterized by the presence of inclusions of hyperphosphorylated human Tau. The claims of the elected invention, however, are drawn only to the nucleic acid vector used to express human Tau in neurons.

Applicant's arguments with respect to the enable rejection set forth on pages 3-8 of the previous office action, have been fully considered and are not persuasive. Applicant argues that the specification teaches that DNA sequences that drive expression to neurons are well known in the art and therefore it is Applicant's position that the specification is enabling for use of any promoter in directing the expression of human Tau. Additionally, the skilled artisan could derive and construct such sequences. Therefore, Applicant is arguing that the specification provides adequate guidance to make and use the claimed nucleic acid comprising any promoter such that when introduced into an animal, the desired phenotype is obtained for the intended use of modeling Alzheimer's disease (see page 2, paragraph 3 of the instant specification).

Applicant also argues that the specification provides ample guidance to prevent expression of endogenous Tau in a broad number of species. Applicant argues that the specification "provides ample guidance to those skilled in the art that the claimed nucleic acid would have the claimed effect of preventing endogenous Tau expression and cause Tau-hyperphosphorylation in the broad number of animal species encompassed by the claims" (paragraph bridging pages 10-11 of Applicant's response). Applicant argues that the specification teaches that incorporation of the nucleic acid sequences into the vector for subsequent integration into the genome of a non-human animal is carried out by procedures well known to the skilled artisan as provided in Sambrook et al. , Molecular Cloning, A Laboratory

Manual, Cold Spring Harbor Press, refer to page 11 of Applicant's response. Applicant also refers to teachings in the specification with respect to antisense technology. The relevance of this excerpt is unclear and Applicant fails to point out its relevance.

Finally, Applicant states that there is sufficient guidance in the specification to permit one of skill in the art to apply ES cell technology to make and use the cells encompassed by the claims.

It should be noted that each of Applicant's references to the specification are in error, however, the sections referred to were identified upon further inspection of the specification.

In response, Applicant's arguments are insufficient to overcome the unpredictability set forth in the art with respect to promoter activity and the resulting phenotype in transgenic animals. For example, Cameron (1997, Molec. Biotech. Vol. 7, pages 253-265) teaches the unpredictability of promoter activity in transgenic animals (paragraph bridging col. 1-2, page 256; refer also to previous office action mailed 02/11/2004; Houdebine, 1994) while Mullins (1993) supports that this variation is enhanced between species (page 632, col. 1, paragraph 4). Specifically, the Thy1 promoter, used in the instant invention, has been demonstrated to exhibit a wide range of activity level in transgenic mice (refer to Sommer, 2000, Experimental Gerontology, Vol. 35, pages 1389-1403). While it is agreed that there are many promoters available to the skilled artisan that are normally active in neurons, the specification fails to provide the guidance necessary to overcome the unpredictability of promoter activity in transgenic animals such that one could predictably generate animals using the claimed vector such that the appropriate levels of Tau are expressed in combination with endogenous or exogenous kinases such that Tau is hyperphosphorylated. The specification teaches that the Thy1

promoter expresses human Tau at levels that, when in combination with expression of exogenous GSK-3β, Tau is hyperphosphorylated. The specification does not teach use of any other promoter. Therefore, the teachings in the specification do not overcome the unpredictability of promoter activity such that the skilled artisan can make and use the claimed nucleic acid vector comprising any promoter to make any species of animal wherein the animal exhibits a useful phenotype, including Tau hyperphosphorylation, with a reasonable expectation of success.

Claims 1-11 are directed to the nucleic acid having targeting sequences such that endogenous Tau is not expressed in an animal. Therefore, the use of the claimed nucleic acid is in making an animal. As set forth in the previous office action, at the time of filing, targeted gene insertion technology to generate a transgenic animal was only available for mouse. In response to Applicant's argument that the specification discloses that Sambrook teaches how to incorporate the nucleic acid sequences into a vector for subsequent integration into the genome of a non-human animal, while Sambrook may teach how to make such a vector, Sambrook does not teach how to specifically insert the vector into the genome of an animal by homologous recombination. Gene targeting in an animal is accomplished by insertion of a transgene into the genome of a totipotent ES and subsequently using said ES to generate an animal whose germ and somatic cells all comprise the insertion. The necessary technology and totipotent ES cells are not currently available for any non-mouse species (refer to previous office action at pages 6-7; Campbell and Wilmut, 1997; Moreadith, 1997; Pera, 2000, Journal of Cell Science, Vol. 113, pages 5-10). The claim is drawn to a vector with a targeting sequence facilitating integration into the genome of an animal. The only species of animal that can be made through gene targeting are mice. Therefore, the scope of claim 1 should be limited to mouse. Accordingly, as claims 20-23

encompass cells in vivo, these claims are not enabled for the reasons set forth above. Therefore the specification is not enabling for making or using the claimed vector comprising a targeting sequence which facilitates integration of said vector into the genome of any species of animal other than mouse or for the use of cells in vivo. It would require undue experimentation for one of skill in the art at the time of filing to make and use the claimed nucleic acid vector to target the vector into the Tau gene of the genome of any non-mouse species of animal or the cells, in vivo, comprising the claimed vector.

Furthermore, claim 1 is drawn to a nucleic acid vector merely comprising a nucleic acid encoding human Tau and a nucleic acid sequence capable of directing expression of human Tau in the nervous system. The claims, as written do not require operable linkage between the sequence capable of directing expression and the human Tau gene. Without specifying operable linkage, the claims read on the mere presence of the two nucleic acids in a single vector. Without operable linkage, the human Tau gene would not be expressed. One of skill in the art would not know how to use the claimed vector that does not lead to expression of human Tau in the nervous system.

Claim 1 does not require that expression of the human Tau gene is directed by a nucleic acid sequence. Claim 1 merely requires that a sequence be capable of directing human Tau expression. Any nucleic acid sequence is capable of directing gene expression if altered by additional elements. The specification fails to enable using a nucleic acid that is merely capable of directing expression of a gene. The specification is enabling for the Thy1 promoter which does direct expression in the nervous system of a mouse. It would require undue experimentation for the skilled artisan to determine how to use the claimed nucleic acid comprising a sequence

that is merely capable of driving expression because one of skill in the art would not know what would need to be done to said sequence capable of driving expression to make it actually drive expression.

Claim 23 encompasses both totipotent and pluripotent ES cells. As set forth above and by Campbell and Wilmut, 1997 and Moreadith, 1997 and Pera, 2000, the state of the art at the time of filing was that totipotent ES cell were only available for mouse. The specification fails to overcome the underdeveloped state of the art as it fails to provide guidance with respect to how to isolate totipotent ES cells form any species of animal other than mouse.

In view of the state of the art with respect to the unpredictability of phenotype of transgenic animals, the unpredictability of promoter activity in transgenic animals, and the underdeveloped art of ES cells at the time of filing, there is insufficient guidance in the specification to make and use the claimed nucleic acid and cells. Thus, for the reasons given above, it would require undue experimentation for one of skill in the art at the time of filing to implement the invention as claimed with a reasonable degree of success.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-12 and 20-23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record set forth on page 9, paragraph 2 of the previous office action mailed 02/11/04.

Applicant argues that amendments to claim 1 obviate any basis for the rejection. This argument is not persuasive. Claim 1 still reads on expression of a protein rather than expression of a gene. Claims 6-9 were not previously included in this rejection as claim 6 lacked dependency on claim 1. As amended, however, claim 6 depends from claim 1. Therefore, claims 2-11 and 20-23 depend from claim 1 and are included in this rejection.

The claims recite that the nucleic acid is capable of directing expression. It is unclear whether expression actually occurs or that the nucleic acid could potentially drive expression upon modification or treatment by certain conditions. "Capable of" implies a latent property and the conditions for the latent property must be clearly defined. Therefore, it is unclear if the latent property is ever obtained.

The rejection of claim 22 for the lack of clarity of the phrase "embryo cell" is withdrawn in light of Applicant's amendment to the claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

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